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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/694,436	10/27/2003	Kathleen C.M. Campbell	SIU 7397	8942

321 7590 04/17/2006

SENNIGER POWERS
ONE METROPOLITAN SQUARE
16TH FLOOR
ST LOUIS, MO 63102

EXAMINER	
GEMBEH, SHIRLEY V	
ART UNIT	**PAPER NUMBER**
1614	

DATE MAILED: 04/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/694,436	CAMPBELL, KATHLEEN C.M.	
	Examiner	Art Unit	
	Shirley V. Gembeh	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-19 and 22-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-19 and 22-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/15/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of claims

Claims 1, 3-20, 22-34 are pending.

Claims 1, 2-20, 22-34 are rejected.

Receipt is acknowledged of amendment filed 20. January 2006. In the amendments filed 20 January 2006, claims 1, 3, 20, and 22 were amended. New claims 33 and 34 added.

Claims 1, 3-20, and 22-34 are pending in this application.

Claims 2 and 21 are cancelled.

Claims 1, 3-20, and 22-34 are rejected.

Response to Arguments

The response filed 20th January 2006 has been received and entered. The text of those sections of Title 35 U.S. Code not included in this action can be found in the prior Office action.

Double Patenting

Applicant's arguments, see page 8, filed 20th January 2006, with respect to non-obviousness type double patenting have been fully considered and are persuasive. The rejection has been withdrawn.

Claim Rejections - 35 USC § 102

Applicant's arguments, with respect to 35 U.S.C. 102 have been fully considered and are persuasive. The rejection has been withdrawn.

Maintained Claim Rejections - 35 USC § 103

Applicant's arguments filed 20th January 2006 have been fully considered but they are not persuasive. Applicant argues that the combination of Campbell and Gabrilove does not teach the instant claimed subject matter.

In response to applicant's argument that, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). Next, it has been held that a prior art reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the applicant was concerned, in order to be relied upon as a basis for rejection of the claimed invention. See *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443 (Fed. Cir. 1992). In this case, Gabrilove specifically teaches treating mucositis administering a methionine related compound. One of ordinary skill in the art would have combined the Campbells' patent with that of Gabrilove to treat mucositis because in the Campbells patent even though it did not expressly teach mucositis, however, gastrointestinal toxicity is a result from GI distress from chemotherapy an obvious variation of mucositis. (Mucositis is the swelling, irritation, and ulceration of the mucosal cells that line the digestive

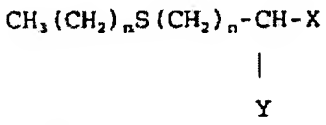
tract. Mucositis can occur anywhere along the digestive tract from the mouth to the anus).

The rejection in the prior office action is maintained and hereby repeated.

Claim1 rejected under 35 U.S.C. 103(a) as being unpatentable over Cambell US 6,265,386 B1 in view of Gabrilove US 4,961,926.

Cambell teaches as to current claims 1 and 20 administering a compound methionine and structurally related compounds (abstract, and at col. 1 line 21-22), exposed to radiation.

- Claims 2 and 21 wherein the protective agent having the structural formula



wherein m is an integer from 0 to 3; n is an integer from 1 to 3; X = $-OR^1$, $-OCOR^1$, $-COOR^1$, -CHO, $-CH(OR^1)_2$, or $-CH_2OH$; Y = $-NR^2R^3$ or -OH; R^1 = H or a substituted or unsubstituted, straight or branched chain alkyl group having 1 to 6 carbon atoms; R^2 = H or a substituted or unsubstituted, straight or branched chain acyl group having 1 to 6 carbon atoms; and R^3 = H or a substituted or unsubstituted, straight or branched chain acyl group having 1 to 6 carbon atoms; or

a pharmaceutically acceptable salt thereof.

at col. 14 lines 30-44.

- Claims 3-6 and 22 wherein the protective agent is D-methionine, L-methionine, D, L methionine etc., at col. 15 line 25+

- claims 4- 9,16, 23-26 and 29-30 wherein the compound is administered prior (radiation/anti-tumor platinum-compound), simultaneously and subsequently at col. 19 lines 7-15.

- claims 10- 12 wherein the protective agent is administered 6 hours before at col.20 line9, 1 hour before to about 1 hour after as in claim 11 at col. 20 line 10, and one and half hour as in current claim 12 at col. 20 line 19.

- claims 13-15,17 and 26-28 administered orally, parenterally or topically at col. 20 line 25+, parenterally administration in the range of from about 1.0 to about 600 is disclosed in the reference as from about 1-to about 500 which is well within applicants claim at col. 20 line 47+ in a blood serum level equivalent to that achieved by parenterally at col. 19 lines 45+.

Although the above cited reference did not explicitly teach the supplement amount of the protective agent in the blood serum to be 10%, 20% or 70% as recited in current claims 18-19 and 31-32, the reference however teaches levels of the protective agent of the blood serum level as claimed but however teaches blood serum level equivalent to that achieved by parenterally at col. 19 lines 45+, nor did the reference teach mucositis (inflammation of the mucosal organ) but teaches gastrointestinal which is a mucosal organ.

Gabrilove teaches a method of preventing mucositis administering methionine at col.3 line 3 in the form of a granulocyte colony stimulating factor.

It would have been obvious for the one of ordinary skill in the art to combine the teachings of Campbell with that of Gabrilove, substitute the compound of Gabrilove with that of Campbell to treat mucositis, as it is known

from the teaching of Gabrilove where an analog containing the same amino acid sequence having an additional methionine was used to treat mucositis.

One of ordinary skill in the art would have been motivated combine the teachings of the above cited prior art and expect a successful result in doing so as successful result has been shown in humans and animals that use methionine before or after exposure to radiation or platinum-containing chemotherapeutic agents. Methionine compounds have been used as protective agents to protect against gastrointestinal disorders.

Thus, the claimed invention was prima facia obvious to make and use at the time the invention was made.

New Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating gastrointestinal toxicity, does not reasonably provide enablement for preventing all types of mucositis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

For rejections under 35 U.S.C. 112, first paragraph, the following factors must be considered (In re Wands, 8 USPQ2d 1400, 1404 (CAFC, 1988)):

1) Nature of invention.

2) State of prior art.

3) Quantity of experimentation needed to make or use the invention based on the content of the disclosure

4) Level of predictability in the art.

5) Amount of direction and guidance provided by the inventor.

6) Existence of working examples.

7) Breadth of claims.

8) Level of ordinary skill in the art.

See below:

In the instant case, applicants are claiming a method of preventing mucositis in a human or animal patient.

1) Nature of the invention.

The nature of the invention is method of preventing mucositis in a human or animal exposed to radiation administering the instant compound to a patient (mammal/animal) in need thereof.

2) State of the prior art and the predictability or lack thereof in the art.

The state of the prior art is that it mucositis occurs when cancer treatments break down the rapidly divided epithelial cells lining the GI tract leaving the mucosal tissue open to ulceration and infection. Schwenka et al indicates prevention will not stop mucositis from occurring (see enclosed

reference page 2). Next, the state of the art involves screening *in vitro* and *in vivo* to determine which compounds exhibited the desired pharmacological activities (i.e. what compounds can treat which specific disease). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face. The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher,* 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statue. Further, their mode of action is often unknown or very unpredictable and administration of the drugs can be accompanied by undesirable side effects.

3) Quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The quantity of experimentation needed is undue experimentation. One of ordinary skill in the art would first need to determine the type of mucositis (oral or gastrointestinal) disease to be treated, and then determine which of the thousands of compounds would be suitable for said treatment and/or prevention.

4) Level of predictability in the art.

The art pertaining to the prevention of mucositis conditions remain highly unpredictable. As disclosed above, there is no prevention that will stop mucositis from occurring).

5) Amount of direction and guidance provided by the inventor.

The amount of direction or guidance present is found on pages 44-48 wherein *in vivo* treatment was used to identify and evaluate mucositis However, that embraces a myriad of conditions. In addition, the gap between *in vitro* activity and *in vivo* utility is large enough to warrant thorough and compelling *in vivo* or clinical data. The example showed on page 40 of 15/15 animals survived is not large enough to warrant prevention of mucositis

6) Existence of working examples.

As discussed above, working example is found on pages 40-18. Applicant's limited working example does not enable one of ordinary skill in the art to treat the numerous amounts of diseases encompassed by the instant invention.

7) Breadth of claims.

Claims 1-34 are extremely broad due to the vast number of possible diseases encompassed by the instant invention.

8) Level of ordinary skill in the art.

The level of ordinary skill in the art is high. Due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by *in vitro* and *in vivo* screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Hence, the specification fails to provide sufficient support of the broad use of the compounds of the claims for the prevention of all mucositis. As a result necessitating one of ordinary skill in the art to perform an exhaustive search to determine which diseases can be treated by what compounds of the instant claims in order to practice the claimed invention.

This rejection can be overcome by reciting specific closely related diseases.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shirley V. Gembeh whose telephone number is 571-272-8504. The examiner can normally be reached on 8:30 -5:00, Monday- Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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4/11/06